REMARKS/ARGUMENTS

This Amendment is submitted in response to the Office Action mailed March 10, 2005. At that time claims 1-4, 7-9, 11-14 and 16-21 were pending in the application. Claims 5 and 6 were withdrawn. In the Office Action, claims 12-14 were objected to under 37 C.F.R. 1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claim. All pending claims were rejected under the written description and enablement requirements of 35 U.S.C. § 112, first paragraph. Claims 1-4, 7-9, 11 and 16-18 were rejected as anticipated under 35 U.S.C. § 102(e), and claims 3, 4, 7 and 16 were rejected under 35 U.S.C. § 102(f). All pending claims were rejected under as obvious under 35 U.S.C. § 103 based on various combinations of references. Claims 3, 4, 7 and 16 were provisionally rejected for obviousness type double patenting.

These rejections are believed to be overcome in part by amendments, and are otherwise traversed for the reasons discussed below.

AMENDMENT TO THE CLAIMS

By this paper, claims 1, 3 and 12 have been amended. Claim 12 has been rewritten into independent form, incorporating, verbatim, language from claim 3 as previously presented. Because the amendment merely incorporates limitations into claim 12 that were, by rule (37 C.F.R. 1.75(c)), already part of claim 12 due to its dependence on claim 3, it does not alter the scope of claim 12 in any way and is not a narrowing amendment. Support for the amendment can be found, for example, in claims 12 and 3 as previously presented.

Claims 1 and 3 have been amended to clarify that it is the *preparations*, not rAAV virions themselves, that are lacking the components necessary to form replication competent adenovirus. As discussed below, this amendment is merely for clarity to prevent an unlikely misreading of the claims as being directed to *rAAV virions* lacking the components necessary to form replication competent adenovirus. Because the amendment merely makes more explicit the interpretation of the claim that would have been clear to one of skill in the art anyway, the amendment does not alter the claim scope in any way and is not a narrowing amendment.

Support for the amendments to claims 1 and 3 can be found, for example, at page 18 of the specification.

Claims 1 and 3 have also been amended to recite that delivery is by intramuscular injection. Support for the amendment can be found, for example, at page 5, line 15 and page 12, line 25, of the specification.

Claims 16-21 have been cancelled.

None of the amendments add new matter.

OBJECTIONS TO THE CLAIMS

Claims 12-14 were objected to under 37 C.F.R. 1.75(c) as being in improper dependent form for failing to further limit the subject matter of a previous claim, in this case claim 3. *See* Office Action at pp. 2-3. However, 37 C.F.R. 1.75(c) clearly states that "[c]laims in dependent form shall be construed to include all the limitations of the claim incorporated by reference into the dependent claim." Claims 12-14 as previously presented did in fact further limit claim 3 by adding administration to a vascular conduit, such as a vein or an artery, none of which limitations are present in claim 3. Claims 12-14 were not broader than claim 3 because they incorporated all the limitations of claim 3 and added additional limitations. Thus claims 12-14, as previously presented, were in proper form.

Nonetheless, solely in order to expedite prosecution, Applicant has rewritten claim 12 in independent form, thereby incorporating the limitation of previous claim 3 that administering of said preparation be "to said muscle cell." Because this limitation was already incorporated into claim 12 by virtue of its dependence on claim 3, this amendment is purely formal and does not alter or limit the scope of claim 12 in any way. Claims 13-14 depend from claim 12, and thus also incorporate the language of claim 12 as amended.

In light of this amendment, Applicant respectfully requests withdrawal of the above referenced objection to the claims.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 1-4 and 7-9, 11-14 and 16-21 were rejected for failure to comply with the written description and enablement requirements of 35 U.S.C. §112, first paragraph. *See* Office Action at pp. 3-12. Applicant respectfully traverses this rejection.

Claims 16-21 have been cancelled.

The Office argues that removal of the limitation "therapeutic effect" from the claims broadens the claims and such that they are not supported by the specification as-filed. Specifically, the Office argues that there is no support for "a general method of delivering and/or expressing a protein encoded by a heterologous nucleic acid." *See* Office Action at p.3.

Achieving a therapeutic effect, however, necessarily requires delivery and expression of the heterologous nucleic acid. It is unreasonable to argue that an application that admittedly contemplates achieving a therapeutic effect does not also contemplate the delivery and expression absolutely necessary to achieve that goal. In addition, the specification discloses uses of the methods of the invention for uses beyond achieving a therapeutic effect, such as creation of transgenic animal models and study to elucidate the physiological or biochemical functions of such heterologous nucleic acids. *See, e.g.*, Specification at page 14, lines 3-21. Because the specification specifically contemplates uses beyond achieving a therapeutic effect, and in any event both delivery and expression are prerequisites for achieving a therapeutic effect, the amendment deleting "therapeutic effect" does not expand the claims beyond their support in the specification.

The Office further argues that the claims do not enable using a genus of administration routes. Claims 1 and 3 have been amended to recite "intramuscular injection" and claim 12 has been rewritten into independent form but retaining its limitation to administering "by way of administration to a vascular conduit of said mammalian subject." Although the Office asserts that the specification discloses only i.m. administration (Office Action at p.8), the specification specifically discloses "administration into the bloodstream by injection . . . by injection into a vein, artery, or any other vascular conduit such as a venule, an arteriole, or capillary." Specification at p.12. The specification further discloses administration by isolated limb perfusion. *Id.*

In light of these amendments to the claims, Applicant requests withdrawal of the rejection based on non-enablement of a genus of administration routes.

In arguing non-enablement, it is stated in the Office Action that "the only asserted use for delivering a heterologous nucleic acid or expressing a protein encoded by a heterologous nucleic acid . . . is for treating disease." *See* Office Action at p.4. However, as mentioned *supra*, numerous non-therapeutic uses are disclosed at page 14 of the specification as filed. The Office predicates it's subsequent evaluation of the claims for enablement based on this incorrect premise. *See* Office Action at p.5. Subsequent discussion of the alleged unpredictability and non-utility of gene therapy is, therefore, inapposite.[1]

The Office acknowledges the disclosure of additional uses at page 14, but then dismisses this disclosure, citing M.P.E.P. § 716.01(c). *See* Office Action at p.13. The cited section of the MPEP, however, deals with objective evidence of non-obviousness, not disclosure in the specification. The disclosure at page 14 of the specification is the antithesis of "attorney's argument" since it is actual disclosure in the specification as filed. The specification clearly enables delivery of a heterologous nucleic acid to animals (*see* example 2 and 3, and figure 1), which animals could then be used for research purposes as disclosed at page 14. For example, the decrease in whole blood clotting time from >60 minutes to 13 minutes reported in example 3 (page 21) is a concrete example of an "alteration of the functioning of cells, tissues, organs or organ systems" referenced at page 14.

In addition, the Office argues that the specification is not enabling of delivery of certain large genes because AAV virions have a packaging size limit of approximately 5kb. As pointed out by Applicant in previous responses, the specification need not enable all possible embodiments of the invention, and the existence of a reasonable number of inoperative embodiments within the scope of the claims is permitted. In addition, the pertinent question with regard to the presence of inoperative embodiments is "whether a skilled person could determine

[1] Applicant notes that in any event, general assertions of the potential problems with gene therapy, or its unpredictability, cannot overcome the factual evidence in the specification that Applicant did, in fact, succeed in delivering and expressing heterologous nucleic acids. *See* figure 1, and examples 2 and 3, of the specification as-filed. The Office itself states that the specification is "enabling for a method of expressing Factor IX in a mammal using an rAAV virion . . . ." *See* Office Action at p.4.

which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." M.P.E.P. § 2164.08(b), *citing Atlas Powder Co.* v. *E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984). It would be readily apparent to one of skill in the art whether or not a gene of interest would fit in an AAV vector, given the known packaging limit, and the skilled person would be required to expend no effort other than to look at the length of the sequence to decide whether or not to pursue AAV-mediated delivery. Because one of skill in the art would be able to determine which embodiments would be inoperative, the claims are not rendered invalid for encompassing those embodiments.

Furthermore, under the Office's present analysis it would have been virtually impossible to ever obtain a patent on conventional AAV-directed gene delivery, since only inventions that overcome the packaging limitation would be properly enabled. Not only is this result unreasonable, it also conflicts with the broad array of AAV gene delivery patents issued by the USPTO to date.

In light of the amendments to the claims, and the arguments presented above, applicant respectfully requests withdrawal of the rejections of claims 1-4, 7-9 and 11-14 under 35 U.S.C. § 112, first paragraph.

REJECTION OF CLAIMS 1-4, 7-9, 11 AND 16-18 UNDER 35 U.S.C. §102(e)

Claims 1-4, 7-9, 11 and 16-18 were rejected under 35 U.S.C. §102(e) as being anticipated by High et al. (U.S. Pat. No. 6,039,392). *See* Office Action at p.16. Applicant respectfully traverses this rejection.

Claims 16-18 have been cancelled.

As previously presented, all pending claims recited "providing a preparation of recombinant adeno-associated virus (rAAV) virions lacking the components necessary to form replication competent adenovirus." The Office admits that High et al. does not teach production of a preparation of AAV virions, wherein the *preparation* lacks the components necessary to form replication competent adenovirus. *See* Office Action at p.4. Nonetheless, the Office argues that the claims as previously presented were ambiguous because it is not clear whether the

claims, as written, were directed to (1) *preparations* that are free of components necessary to form replication competent adenovirus, or (2) *rAAV virions* that are free of components necessary to form replication competent adenovirus. The Office argued that under interpretation (2), High et al. anticipates the claimed invention because "AAV vectors do not have components necessary to form replication competent adenovirus."

However, one of skill in the art would not interpret the claims under interpretation (2) because that interpretation completely nullifies the element "lacking the components necessary to form replication competent adenovirus." Interpretation (2) makes no sense in context because it presupposes that rAAV virions (rather than *preparations* of rAAV virions) might comprise components necessary to form replication competent adenovirus. Although it is linguistically possible to construe the wording of the claims as previously presented to arrive at the Office's interpretation (2), it would be clear to one of skill in the art that interpretation (1) is the only reasonable reading. This is particularly true when it is realized that the claims are read in light of the specification, which provides a method for producing adenovirus-free rAAV preparations.

Nonetheless, solely in order to advance prosecution, Applicant has amended claims 1 and 3 to clarify that it is the *preparation*, rather than the rAAV virions, that are lacking the components necessary to form replication competent adenovirus. In light of the argument presented and the amendment to the claims, Applicant requests that the rejection under 35 U.S.C. §102(e) based on High et al. be withdrawn.

REJECTION OF CLAIMS 3, 4, 7 AND 16 UNDER 35 U.S.C. §102(e)

Claims 3, 4, 7 and 16 were rejected under 35 U.S.C. §102(e) as being anticipated by Miller et al. (U.S. Pat. Pub. No. 2004/0248288). *See* Office Action at p.17. Applicant respectfully traverses this rejection.

Claim 16 has been cancelled, and claim 3 (and thus 4 and 7) has been amended to recite that administering is "by intramuscular injection." Miller et al. discloses packaging cell lines for efficient production of AAV virions, and further discloses methods for producing such cell lines and for producing AAV virions useful for gene therapy. *See* Miller et al. at Abstract. Although the specification teaches methods of producing AAV virions having AAV-6 capsid proteins, and

provides a method of producing such AAV virions without use of infectious adenovirus particles, it does not disclose administering a preparation of rAAV virions to muscle cells by intramuscular injection as recited in claim 3 (as amended). The only reference to muscle cells in Miller et al. is to transduction of smooth muscle cells incidental to administration of rAAV virions to airway epithelial cells. In nearly every case, the data in figures 4 and 5 of Miller et al. show that transduction of muscle is less efficient than transduction of any other tissue examined.

In light of the arguments presented and the amendment to the claims, Applicant requests that the rejection under 35 U.S.C. §102(e) based on Miller et al. be withdrawn.

REJECTION OF CLAIMS 3, 4, 7 AND 16 UNDER 35 U.S.C. §102(f)

Claims 3, 4, 7 and 16 were rejected under 35 U.S.C. §102(f) because allegedly applicant did not invent the claimed subject matter. *See* Office Action at p.18. Applicant respectfully traverses this rejection.

The Examiner cites U.S. Patent Application No. 10/169,785, which is the same application cited as a reference under 35 U.S.C. §102(e) as Miller et al. Claim 16 has been cancelled.

Pursuant to M.P.E.P. § 706.02(g), "[t]he examiner must presume the applicants are the proper inventors unless there is proof that another made the invention and that the applicant derived the invention from the true inventor." The Office has provided no such evidence of derivation, and thus rejection under 35 U.S.C. §102(f) is improper.

In addition, Miller does not invalidate claims 3, 4 and 7 for the reasons stated *supra* with regard to the rejection under 35 U.S.C. §102(e), *i.e.*, that Miller does not disclose administration by intramuscular injection.

In light of the argument presented and the amendment to the claims, Applicant requests that the rejection under 35 U.S.C. §102(f) based on Miller et al. be withdrawn.

REJECTION UNDER 35 U.S.C. §103(a)

Claims 3, 4 and 16-17 were rejected under 35 U.S.C. §103(a) as being obvious over Russell et al. (U.S. Pat. No. 6,156,303) in view of Matsushita et al. (*Gene Therapy* (1998) 5: 938-45). *See* Office Action at p.20. Claims 16 and 17 have been cancelled.

Claims 1-4, 7-9, 11 and 16-18 were rejected under 35 U.S.C. §103(a) as obvious over High et al. (U.S. Pat. No. 6,093,392) taken with Matsushita et al. Office Action at p.22. Claims 16-18 have been cancelled.

Claims 3, 12-14, 16 and 19-21 are rejected under 35 U.S.C. §103(a) as being obvious over High et al. (U.S. Pat. No. 6,093,392) taken with Matsushita et al., or Russell et al. (U.S. Pat. No. 6,156,303) taken with Matsushita et al., and *further in view of* Cuoto et al. (U.S. Pat. No. 6,221,349). *See* Office Action at p. 24. Claims 16 and 19-21 have been cancelled.

Applicant respectfully traverses these rejections.

M.P.E.P. § 2142 provides that in order to establish a *prima facie* case of obviousness, the Office must provide (*inter alia*) some suggestion or motivation, either in the references themselves of in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the teachings. The mere fact that references might be combined does not render the resulting combination obvious absent some suggestion to make the claimed combination. *See In Re Bergel,* 292 F.2d 955, 956-57 (CCPA 1961). The requirement for motivation or suggestion is intended to prevent the use of impermissible hindsight in determining the obviousness or non-obviousness of an applicant's invention. *See In re Lee,* 277 F.3d 1338, 1343 (Fed. Cir. 2002) (*citing In re Dembiczak,* 175 F.3d 994, 999 (Fed Cir. 1999)).

All three obviousness rejections rely on the combination of Matsushita with other references. Matsushita is cited to provide the element of preparations of rAAV virions lacking the components necessary to form replication competent adenovirus. In all of the rejections, the only proposed suggestion or motivation for combination of the references is that the method of AAV virion production disclosed in Matsushita results in a safer preparation, and that large-scale production is less complicated. These statements are more properly characterized as a motivation to *use* the Matsushita method in general, rather than a motivation to *combine* Matsushita's method with the other elements of the claimed invention.

Case law is clear that motivation or suggestion to combine references must be specific and particular. *In re Lee*, 277 F.3d 1338 (Fed. Cir. 2002) ("The need for specificity pervades this authority"). Cases express the need for specificity in different ways, but all require that there be motivation to make the specific combination of the claimed invention. The requirement is expressed variously as "some motivation, suggestion, or teaching of the desirability of making *the specific combination that was made by the applicant*" (*In re Dance*, 160 F.3d 1339, 1343 (Fed. Cir. 1998)), that one of skill "would have selected *these components* for combination *in the manner claimed* (*In re Kotzlab*, 217 F.3d 1365, 1371 (Fed. Cir. 2000)) (both cited in *In re Lee*; all emphases added). Mere conclusory statements regarding motivation are insufficient. *See In re Lee*, 277 F.3d at 1333, 1341-43 (noting that mere assertions that one cited reference in an obviousness rejection was "user friendly" and that it "functions as a tutorial" do not adequately address the issue of a motivation to combine the reference with another). Because the general advantages cited for the method of Matsushita do not suggest the claimed invention, there is no motivation to combine, and thus no *prima facie* case of obviousness.

The over-breadth of the Office's arguments is best illustrated by considering its consequences. Under the Office's approach, essentially all combination inventions would be obvious because mere general statements of improved utility of a given element would be sufficient motivation to render obvious *any* combination of that element with any other element(s). Publications (such as Matsushita), and particularly patent applications, almost invariably include general statements of the advantages of the disclosed subject matter over the prior art. To assume that these commonplace self-laudatory statements render all combinations obvious would vitiate the requirement for motivation/suggestion altogether. If motivation were so easy to find as the Office's argument suggests, it would simply cease to exist as a meaningful impediment to impermissible hindsight.

Because there is no motivation to combine Matsushita with the other cited references, the proposed *prima facie case* of obviousness must fail. Accordingly, withdrawal of the rejections of claims 1-4 and 7-9 and 11-14 as obvious under 35 U.S.C. §103(a) is respectfully requested.

DOUBLE PATENTING REJECTION

Claims 3, 4, 7 and 16 were provisionally rejected for obviousness type double patenting over claims 37 and 38 of co-pending U.S. Application No. 10/169,785, which is the same application cited as a reference under 35 U.S.C. §102(e) as Miller et al. *See* Office Action at p.26. Applicant respectfully traverses.

Obviousness-type double patenting arises when a claim in a subject application is not patentably distinct from the subject matter claimed in another application that shares at least one common inventor or is commonly owned. It is only the claims, and not the specification, of the cited reference that is to be considered in making an obviousness-type double patenting rejection. *See General Foods Corp.* v. *Studiengesellschaft Köhle*, 972 F.2d 1272, 1275 (Fed. Cir. 1992) ("the law of double patenting is concerned only with what is claimed"). Although the specification may be used as a dictionary to define claim terms, "[w]hen considering whether the invention defined in a claim of an application is an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art." M.P.E.P. § 804 (at 800-22).

Claim 37 of Miller et al. relates to a method or transducing airway epithelial cells with an AAV comprising AAV-6 capsid. Claim 3 (and thus 4 and 7) of the instant application relates to a method of delivering a heterologous nucleic acid to at least one muscle cell using a preparation of rAAV virions comprising AAV-6 capsids, said preparations being free of components necessary to form replication competent adenovirus. Claim 3 of the instant application does not recite transfection of airway epithelial cells, and claims 37 and 38 of Miller et al., and as noted by the Office, "do not specifically recite expressing the gene of interest in at least one muscle cell." *See* Office Action at p.26. These differences between the claims prove that they are patentably distinct, and that an obviousness type double patenting rejection is improper.

In an attempt to establish obviousness, the Office argues that the claimed method (transduction of airway epithelial cells) "results in delivery of the AAV to muscle cells and expression of the gene in said muscle cells." *See* Office Action at p.27. This resort to the specification to supply the element missing from the claims is not permitted, and goes far beyond use of the specification as a dictionary. The low-level transduction of smooth muscle cells in the

airway that is disclosed in the specification is not used to "define" any claim term. In a double patenting analysis, the claims of the cited reference are to be viewed for what they *define*, not what they disclose. *See General Foods*, 972 F.2d at 1281 and references cited therein.

Accordingly, Applicant requests and the provisional obviousness-type double patenting rejection be withdrawn.

CONCLUSION

Applicants respectfully assert that claims 1-4, 7-9 and 11-14 are patentably distinct from the cited references, and request that a timely Notice of Allowance be issued in this case. If there are any remaining issues preventing allowance of the pending claims that may be clarified by telephone, the Examiner is requested to call the undersigned.

Respectfully submitted,

Kevin B. Laurence
Reg. No. 38,219
Attorney for Applicant

Date: September 12, 2005

STOEL RIVES LLP
One Utah Center
201 South Main Street, Suite 1100
Salt Lake City, UT 84111
Telephone: (801) 578-6992
Facsimile: (801) 578-6999